

ANDA 74-650

DEC 29 1997

Hi-Tech Pharmacal Co., Inc.  
Attention: Elan Bar-Giora  
369 Bayview Avenue  
Amityville, NY 11701

Dear Sir:

This is in reference to your abbreviated new drug application dated March 20, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sulfamethoxazole and Trimethoprim Oral Suspension USP, 200 mg/40 mg per 5 mL.

Reference is also made to your amendments dated April 28 and 30, September 3 and 4, 1997, and November 19, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sulfamethoxazole and Trimethoprim Oral Suspension USP, 200 mg/40 mg per 5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Bactrim™ Pediatric Suspension of Hoffman-La Roche Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

*per 12/29/97*  
Douglas L. Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**H-T****H-T**

NDC 50383-824-16

SULFAMETHOXAZOLE  
AND  
TRIMETHOPRIM  
ORAL SUSPENSION, USP  
200 mg / 40 mg per 5 mL

**SULFAMETHOXAZOLE  
AND  
TRIMETHOPRIM  
ORAL SUSPENSION, USP  
200 mg / 40 mg per 5 mL**

**CAUTION:** Federal law  
prohibits dispensing  
without prescription.

Each teaspoonful (5 mL) contains:  
Sulfamethoxazole ..... 200 mg  
Trimethoprim ..... 40 mg  
Alcohol ..... 0.26%

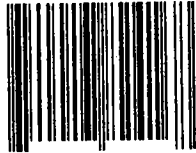
**USUAL DOSAGE:** See package insert for dosage and full  
prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.  
Store at room temperature 15°-30°C (59°-86°F). Protect from light.

**SHAKE WELL BEFORE USING.**

16 fl oz (473 mL)

HI-TECH PHARMACAL CO., INC.  
Amityville, NY 11701

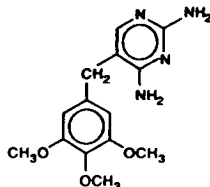


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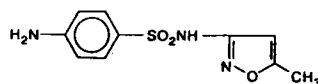
# DESCRIPTION

Sulfamethoxazole and Trimethoprim Oral Suspension is a synthetic antibacterial combination product. Each teaspoonful (5 mL), for oral administration, contains 200 mg sulfamethoxazole and 40 mg trimethoprim in a vehicle containing alcohol 0.26%, methylparaben 0.1% and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid (anhydrous), FD&C Red No. 40, and FD&C Blue No. 1, flavor, glycerin, microcrystalline cellulose, polyorbate 80, saccharin sodium, sorbitol and water.

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. It is a white to light yellow, odorless, tasteless, bitter compound with a molecular weight of 290.3, and the molecular formula  $C_{14}H_{18}N_4O_3$ . The structural formula is:



Sulfamethoxazole is N<sup>1</sup>-(5-methyl-3-isoxazolyl)sulfanilamide. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28, and the molecular formula  $C_{10}H_{11}N_2O_3S$ . The structural formula is:



## CLINICAL PHARMACOLOGY

Sulfamethoxazole and trimethoprim is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominantly by N<sub>4</sub>-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3- and 4'-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be therapeutically active forms. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see DOSAGE AND ADMINISTRATION section). Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. During administration of 160 mg trimethoprim and 800 mg sulfamethoxazole b.i.d., the mean steady state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady state mean plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68.0 mcg/mL, respectively. These steady state levels were achieved after three days of drug administration.<sup>1</sup>

Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of trimethoprim and sulfamethoxazole is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N<sub>4</sub>-acetylated metabolite.<sup>2</sup> When administered together as sulfamethoxazole and trimethoprim oral suspension, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both trimethoprim and sulfamethoxazole distribute to sputum, vaginal fluid, and middle ear fluid; trimethoprim also distributes to bronchial secretion and both pass the placental barrier and are excreted in breast milk.

**Microbiology:** Sulfamethoxazole inhibits bacterial synthesis of dihydrolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrolic acid from dihydrolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

*In vitro* studies have shown that bacterial resistance develops more slowly with sulfamethoxazole and trimethoprim than with either trimethoprim or sulfamethoxazole alone.

*In vitro* serial dilution tests have shown that the spectrum of antibacterial activity of sulfamethoxazole and trimethoprim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *Proteus mirabilis* and indole-positive *Proteus* species including *Proteus vulgaris*. The usual spectrum of antimicrobial activity of sulfamethoxazole and trimethoprim includes the following bacterial pathogens isolated from middle ear exudate and from bronchial secretions: *Haemophilus influenzae*, including ampicillin-resistant strains, and *Streptococcus pneumoniae*, *Shigella flexneri* and *Shigella sonnei* are usually susceptible. The usual spectrum also includes enterotoxigenic strains of *Escherichia coli* (ETEC) causing bacterial gastroenteritis.

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATION VALUES FOR  
SULFAMETHOXAZOLE AND TRIMETHOPRIM SUSCEPTIBLE ORGANISMS (MIC-mcg/mL)

Bacteria	TMP Alone	SMX Alone	TMP/SMX (1:20)	
			TMP	SMX
<i>Escherichia coli</i>	0.05-1.5	1.0-245	0.05-0.5	0.95-9.5
<i>Escherichia coli</i> (enterotoxigenic strains)	0.015-0.15	0.285-950	0.005-0.15	0.095-2.85
<i>Proteus</i> species (indole positive)	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
<i>Morganella morganii</i>	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
<i>Proteus mirabilis</i>	0.5-1.5	7.35-30	0.05-0.15	0.95-2.85
<i>Klebsiella</i> species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
<i>Enterobacter</i> species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
<i>Haemophilus influenzae</i>	0.15-1.5	2.85-95	0.015-0.15	0.285-2.85
<i>Streptococcus pneumoniae</i>	0.15-1.5	7.35-24.5	0.05-0.15	0.95-2.85
<i>Shigella flexneri</i> †	<0.01-0.04	<0.16-320	<0.002-0.03	0.04-0.625
<i>Shigella sonnei</i> †	0.02-0.08	0.625-320	0.004-0.06	0.08-1.25

TMP = Trimethoprim; SMX = Sulfamethoxazole

†Rudoy RC, Nelson JD, Hattalin KC, *Antimicrobial Agents Chemotherapy* 5:439-443, May 1974.

The recommended quantitative disc susceptibility method may be used for estimating the susceptibility of bacteria to sulfamethoxazole and trimethoprim.<sup>3,4</sup> With this procedure, a report from the laboratory of "Susceptible to trimethoprim and sulfamethoxazole" indicates that the infection is likely to respond to therapy with sulfamethoxazole and trimethoprim. If the infection is confined to the urine, a report of "Intermediate susceptibility to trimethoprim and sulfamethoxazole" also indicates that the infection is likely to respond. A report of "Resistant to trimethoprim and sulfamethoxazole" indicates that the infection is unlikely to respond to therapy with sulfamethoxazole and trimethoprim.

**SULFAMETHOXAZOLE  
AND  
TRIMETHOPRIM  
ORAL SUSPENSION**

**SULFAMETHOXAZOLE  
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**INDICATIONS AND USAGE**

**URINARY TRACT INFECTIONS:** For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *Proteus mirabilis*, and *Proteus vulgaris*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

**ACUTE OTITIS MEDIA:** For the treatment of acute otitis media in children due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of sulfamethoxazole and trimethoprim in children under two years of age. Sulfamethoxazole and trimethoprim is not indicated for prophylactic or prolonged administration in otitis media at any age.

**ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:** For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim offers some advantage over the use of a single antimicrobial agent.

**SHIGELLOSIS:** For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

**PNEUMOCYSTIS CARINI PNEUMONIA:** For the treatment of documented *Pneumocystis carini* pneumonia. For prophylaxis against *Pneumocystis carini* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *Pneumocystis carini* pneumonia.

**TRAVELERS' DIARRHEA IN ADULTS:** For the treatment of travelers' diarrhea due to susceptible strains of enterotoxigenic *E. coli*.

**CONTRAINDICATIONS**

Sulfamethoxazole and trimethoprim is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. Sulfamethoxazole and trimethoprim is also contraindicated in pregnant patients and nursing mothers because sulfonamides pass the placenta and are excreted in the milk and may cause hemolysis. Trimethoprim and sulfamethoxazole is contraindicated in infants less than two months of age.

**WARNINGS**

**FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.**

**SULFAMETHOXAZOLE AND TRIMETHOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION.** Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions. In rare instances a skin rash may be followed by more serious reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

**SULFAMETHOXAZOLE AND TRIMETHOPRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.** Clinical studies have documented that patients with group A  $\beta$ -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with sulfamethoxazole and trimethoprim than do those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

**PRECAUTIONS**

**General:** Sulfamethoxazole and trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

**Use in the Elderly:** There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see **WARNINGS** AND **ADVERSE REACTIONS** sections) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION** section).

**Use in the Treatment of and Prophylaxis for *Pneumocystis Carini* Pneumonia in Patients With Acquired Immunodeficiency Syndrome (AIDS):** AIDS patients may not tolerate or respond to trimethoprim and sulfamethoxazole in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with sulfamethoxazole and trimethoprim therapy in AIDS patients who are being treated for *Pneumocystis carini* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of trimethoprim and sulfamethoxazole in non-AIDS patients. Adverse effects are generally less severe in patients receiving trimethoprim and sulfamethoxazole for prophylaxis. A history of mild intolerance to trimethoprim and sulfamethoxazole in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis.<sup>5</sup> However, if a patient develops skin rash or any sign of adverse reaction, therapy with trimethoprim and sulfamethoxazole should be reevaluated (see **WARNINGS**).

**Information for Patients:** Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

**Laboratory Tests:** Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole and trimethoprim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

**Drug Interactions:** In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that sulfamethoxazole and trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole and trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole and trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole and trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

**Drug/Laboratory Test Interactions:** Sulfamethoxazole and trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

**Carcinogenesis:** Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole and trimethoprim.

**Mutagenesis:** Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes in vitro with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with sulfamethoxazole and trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole and trimethoprim revealed no chromosomal abnormalities.

**Impairment of Fertility:** No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim and 350 mg/kg/day sulfamethoxazole.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfit and Purcell<sup>6</sup>, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfit and Purcell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, sulfamethoxazole and trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects:** See CONTRAINDICATIONS section.

**Nursing Mothers:** See CONTRAINDICATIONS section.

**Pediatric Use:** Sulfamethoxazole and trimethoprim is not recommended for infants younger than two months of age (see INDICATIONS AND USAGE and CONTRAINDICATIONS sections).

#### ADVERSE REACTIONS

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).

**Hematologic:** Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

**Allergic Reactions:** Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarthritis nodosa and systemic lupus erythematosus have been reported.

**Gastrointestinal:** Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

**Genitourinary:** Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

**Neurologic:** Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

**Psychiatric:** Hallucinations, depression, apathy, nervousness.

**Endocrine:** The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

**Musculoskeletal:** Arthralgia and myalgia.

**Respiratory:** Pulmonary infiltrates.

**Miscellaneous:** Weakness, fatigue, insomnia.

#### OVERDOSAGE

**Acute:** The amount of a single dose of sulfamethoxazole and trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

**Chronic:** Use of sulfamethoxazole and trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored.

#### DOSAGE AND ADMINISTRATION

Not recommended for use in infants less than two months of age.

**Urinary Tract Infections and Shigellosis in Adults and Children, and Acute Otitis Media in Children:**

**Adults:** The usual adult dosage in the treatment of urinary tract infections is four teaspoons (20 mL) Sulfamethoxazole and Trimethoprim Oral Suspension every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

**Children:** The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Children two months of age or older:

Weight		Dose - every 12 hours	
lb	kg	Teaspoonfuls	
22	10	1	( 5 mL)
44	20	2	(10 mL)
66	30	3	(15 mL)
88	40	4	(20 mL)

**For Patients With Impaired Renal Function:** When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

SULFAMETHOXAZOLE  
AND  
TRIMETHOPRIM  
ORAL SUSPENSION

SULFAMETHOXAZOLE  
AND  
TRIMETHOPRIM  
ORAL SUSPENSION

**Acute Exacerbations of Chronic Bronchitis in Adults:**

The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is four teaspoonfuls (20 mL) Sulfamethoxazole and Trimethoprim Oral Suspension every 12 hours for 14 days.

**Pneumocystis Carinii Pneumonia:**

**Treatment: Adults and Children:**

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonia is 15 to 20 mg/kg trimethoprim and 75 to 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 to 21 days<sup>7</sup>. The following table is a guideline for the upper limit of this dosage.

Weight		Dose - every 6 hours	
lb	kg	Teaspoonfuls	
18	8	1	( 5 mL)
35	16	2	(10 mL)
53	24	3	(15 mL)
70	32	4	(20 mL)
88	40	5	(25 mL)
106	48	6	(30 mL)
141	64	8	(40 mL)
176	80	10	(50 mL)

For the lower limit dose (15 mg/kg trimethoprim and 75 mg/kg sulfamethoxazole per 24 hours) administer 75% of the dose in the above table.

**Prophylaxis:**

**Adults:**

The recommended dosage for prophylaxis in adults is four teaspoonfuls (20 mL) of trimethoprim sulfamethoxazole oral suspension daily.<sup>8</sup>

**Children:**

For children, the recommended dose is 150 mg/m<sup>2</sup>/day trimethoprim with 750 mg/m<sup>2</sup>/day sulfamethoxazole given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.<sup>9</sup> The following table is a guideline for the attainment of this dosage in children:

Body Surface Area		Dose - every 12 hours	
(m <sup>2</sup> )		Teaspoonfuls	
0.26		1/2	(2.5 mL)
0.53		1	( 5 mL)
1.06		2	(10 mL)

**Travelers' Diarrhea in Adults:**

For the treatment of travelers' diarrhea, the usual adult dosage is four teaspoonfuls (20 mL) of sulfamethoxazole and trimethoprim oral suspension every 12 hours for 5 days.

**HOW SUPPLIED**

Sulfamethoxazole and Trimethoprim Oral Suspension USP is a purple, grape-flavored suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole per 5 mL (teaspoonful) supplied in 1 pint (473 mL) bottles. (NDC 50383-824-16)

Store at room temperature 15°-30°C (59°-86°F) and protect from light.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Caution: Federal law prohibits dispensing without prescription.

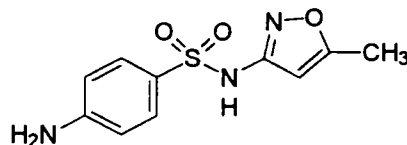
**REFERENCES:**

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9. CDC Guidelines for Prophylaxis against *Pneumocystis carinii* pneumonia for children infected with human immunodeficiency virus. *MMWR*. 1991; 40(RR-2):1-13.

Manufactured by:  
Hi-Tech Pharmacal Co., Inc.  
Amityville, New York 11701

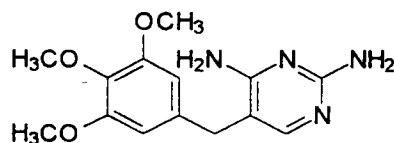
MG #13244  
Rev. 11/87

1. CHEMISTRY REVIEW NO. 3
2. ANDA #74-650
3. NAME AND ADDRESS OF APPLICANT  
Hi-Tech Pharmacal Co., Inc.  
Attention: Elan Bar-Giora  
369 Bayview Avenue  
Amityville, NY 11701
4. LEGAL BASIS for ANDA SUBMISSION  
Approved application for Bactrim™ Oral Suspension  
(Sulfamethoxazole and Trimethoprim Oral Suspension) of Roche Laboratories.
5. SUPPLEMENT(s)  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Sulfamethoxazole and Trimethoprim Oral Suspension USP,  
200 mg/40 mg per 5 mL
8. SUPPLEMENT(s) PROVIDE(s) FOR  
N/A
9. AMENDMENTS AND OTHER DATES  
Original Application Submission Date March 20, 1995  
☒ Amendment Date May 8, 1995  
☒ Major Amendment Date October 4, 1996  
☒ Major Amendment Date November 27, 1996  
☒ Major Amendment Date April 30, 1997 (This Review)  
☒ New Correspondence Date May 1, 1997 (Request to Change  
Deficiencies from Major to Minor)  
☒ Telephone Amendment Date September 3, 1997 (This Review)  
☒ Telephone Amendment Date September 4, 1997 (This Review)
10. PHARMACOLOGICAL CATEGORY  
Antibacterial, Antipneumocystis
11. Rx or OTC  
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM  
Suspension
14. POTENCY  
Sulfamethoxazole, 200 mg/5 mL  
Trimethoprim, 40 mg/5 mL
15. CHEMICAL NAME AND STRUCTURE  
Sulfamethoxazole. C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S. 253.28. Benzensulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl)-. 723-46-6. USP 23, page 1461.



and

Trimethoprim.  $C_{14}H_{18}N_4O_3$ . 290.32. 2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-. 738-70-5. USP 23, page 1602.



16. RECORDS AND REPORTS  
N/A

17. COMMENTS  
See Individual Sections; Comments from deficiency letter are followed by firm's response. The review also includes firm's response to the Tcon. between Mr. James Wilson and the firm (9/3/97), and to the Tcon. between Mr. James Wilson, Dr. Vilayat Sayeed, and the firm (9/4/97).

18. CONCLUSIONS AND RECOMMENDATIONS  
Approvable

19. REVIEWER:  
U.S. Atwal

DATE COMPLETED:  
December 12, 1997

ANDA 74-650 APPROVAL SUMMARY

**DRUG PRODUCT:** Sulfamethoxazole and Trimethoprim Oral Suspension USP,  
200 mg/40 mg per 5 mL.

**FIRM:** Hi-Tech Pharmacal Co., Inc.

**DOSAGE FORM:** Oral Suspension

**STRENGTH:** 200 mg/40 mg per 5 mL

**cGMP STATEMENT/EIR UPDATE STATUS:** EER Acceptable Date August 27, 1997

**BIO STUDY:** APPROVE, Letter Sent on June 12, 1997

**VALIDATION:** DS and DP are compendial

**STABILITY:** Three months accelerated, 40°C, and three months room temperature, 25°C, data in the market package size, 16 oz white HDPE container, provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. All reported data are within specifications as listed. Thus, a 24 month expiration date is justified.

Tests and specifications for the drug product on stability include:

**LABELING:** APPROVE, Review Date 12/2/1997

**STERILIZATION VALIDATION:** (IF APPLICABLE): N/A

**SIZE OF BIO BATCH:** The bio batch, #401824 is also one of the two test batches (#401824, drug substance source, , and #601824, drug substance source, ; Batch size in each case being

**SIZE OF STABILITY BATCHES:** Stability batches are the same as test batches, #401824 and #601824 and one stability batch, #401824, is the bio batch.

**PROPOSED PRODUCTION BATCHES:** The proposed production batch sizes are and The manufacturing process for production batches is the same as that for test batches.

CHEMIST:

DATE: 12/16/97

SUPERVISOR:

DATE:

201  
ANDA 74-650

JUN 12 1997

Hi-Tech Pharmacal Co., Inc.  
Attention: Elan Bar-Giora  
369 Bayview Avenue  
Amityville NY 11701

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Sulfamethoxazole and Trimethoprim Oral Suspension USP, 200 mg/40 mg per 5 mL.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The production batch for marketing this product should not exceed
3. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in a medium of 899 ml of water and 1 ml of 0.2 N HCL, at 37°C, using USP 23 Apparatus II (Paddle) at 50 rpm. The test drug should meet the following specifications:

Not less than (Q) of the labeled amount of each component of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

6/11/1997  
Nicholas Fleischer, Ph.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

JUN 10 1997

Sulfamethoxazole and  
Trimethoprim Oral Suspension  
200mg/40mg per 5ml  
ANDA #74-650  
Reviewer: Sikta Pradhan  
WP #74650AD.N96

Hi-Tech Pharmacal Co. Inc.  
Amityville, New York  
Submission Dated:  
November 27, 1996  
April 28, 1997

**Review of an Amendment to a Bioequivalence Study  
and Dissolution Data**

**Background:**

The firm has previously conducted an in vivo bioequivalence study under fasting conditions in healthy male volunteers on its test product, Sulfamethoxazole (200mg/5ml) and Trimethoprim (40mg/5ml) Oral Suspension USP, and the reference product, Bactrim<sup>R</sup> Oral Suspension (200 mg/40 mg in 5ml) manufactured by Roche Laboratories. The study was found to be incomplete by the Division of Bioequivalence as the firm did not conduct the comparative dissolution testing on the test and reference products.

In this amendment, the firm has provided the comparative dissolution testing data as requested by the Agency on February 15, 1996.

The products employed in the in vivo study are as follows:  
(reviewer: Ramona M. Hawkins)

- (1) Test Product - Trimethoprim (40mg/5ml) and Sulfamethoxazole (200mg/5ml)  
Suspension Lot # 401-824  
Manufacturer: Hi-Tech Pharmacal Co.  
The batch size has been stated as being
- (2) Reference Product - Trimethoprim (40mg/5ml) and Sulfamethoxazole (200mg/5ml)  
(Bactrim) Pediatric Suspension Lot # 2110  
Manufacturer: Roche Laboratories

The firm has conducted the comparative dissolution testing on two lots of the test product produced from raw materials obtained from two different sources. As the first source of raw material (source of bio lot) is no longer available, the firm intends to manufacture their product from the raw materials obtained from the second source. The dissolution testing data are presented below:

**Table 1 In Vitro Dissolution Testing**

**Drug: Sulfamethoxazole and Trimethoprim Oral Suspension**

Dose Strength: **200mg/40mg per 5ml**

ANDA No.:74-650

Firm:Hi-Tech Pharmacal Co. Inc.

Submission Date:November 27, 1996

**I. Conditions for Dissolution Testing:**

**NON-USP, FDA METHOD**

USP XXIII: Paddle: RPM: 50

No. Units Tested: 12

Medium:Dilute HCl (899ml water and 1.0 mL of 0.2N HCl) Volume: 900 mL

Specifications: a 60 minutes both components

Reference Drug: Bactrim<sup>®</sup> Oral Suspension (200 mg/40 mg in 5ml)  
manufactured by Roche Laboratories.

Assay Methodology:

**II. Results of In Vitro Dissolution Testing: Sulfamethoxazole**

Sampling Times (Minutes)	Test Product (produced from raw materials obtained from old source) Lot # 401-824 Strength(mg) 200 mg/5 mL suspension			Reference Product Lot # 2111 Strength(mg) 200 mg/5 mL suspension		
	Mean %	Range	%CV	Mean %	Range	%CV
15	60.5		6.4	86.0		3.3
30	67.1		4.2	86.1		2.6
45	72.0		2.9	85.0		2.3
60	74.9		4.9	85.8		1.9

**III. Results of In Vitro Dissolution Testing: Trimethoprim**

Sampling Times (Minutes)	Test Product (produced from raw materials obtained from old source) Lot # 401-824 Strength(mg) 40 mg/5 mL suspension			Reference Product Lot # 2111 Strength(mg) 40 mg/5 mL suspension		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.8		1.5	104.1		1.1
30	96.2		2.1	105.0		0.8
45	98.0		2.5	105.0		0.8
60	99.1		2.6	104.6		0.9

IV. Results of In Vitro Dissolution Testing: Sulfamethoxazole						
Sampling Times (Minutes)	Test Product (produced from raw materials obtained from 2nd source) Lot # 601-824 Strength(mg) 200 mg/ 5 mL suspension			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	87.9		5.2			
30	85.9		1.8			
45	87.3		2.9			
60	86.7		2.6			
V. Results of In Vitro Dissolution Testing: Trimethoprim						
Sampling Times (Minutes)	Test Product (produced from raw materials obtained from 2nd source) Lot # 601-824 Strength(mg) 40 mg/ 5 mL suspension			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	105.9		1.0			
30	106.1		1.2			
45	105.5		1.1			
60	106.8		1.02			

**Comments:**

1. The firm has previously conducted an acceptable in vivo bioequivalence study under fasting conditions in healthy male volunteers on its test product, Sulfamethoxazole (200mg/5ml) and Trimethoprim (40mg/5ml) Oral Suspension USP, lot# 401-824 (using old raw material) and the reference product, Bactrim<sup>R</sup> Oral Suspension (200 mg/40 mg in 5ml) manufactured by Roche Laboratories.
2. The comparative dissolution testing conducted on the test product, lot# 601-824 **using new raw material** (from new source) and on the reference product, lot# 2111, is acceptable. However, perhaps due to long exposure, the Sulfamethoxazole component of the test lot#, 401-824, manufactured on February 23, 1994 using old source of raw material did not meet the dissolution testing specification in 60 minutes),.
3. There is no change in formulations of two test products produced from two different sources (see table 2, attached).

4. Batch size of the test product on which the bioequivalence study was conducted was only and therefore, the firm should be informed that their production batch for marketing the product should not exceed

**Recommendations:**

1. The in vivo bioequivalence study conducted by Hi-Tech Pharmacal Co, Inc. on its Sulfamethoxazole and Trimethoprim Oral Suspension, 200mg/400mg per 5ml, Lot #401-824, comparing it to Bactrim (Sulfamethoxazole and Trimethoprim) Oral Suspension, 200mg/400mg/5ml manufactured by Roche Laboratories, has been found acceptable to the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product, Bactrim (Sulfamethoxazole and Trimethoprim) Oral Suspension, 200mg/400mg/5ml manufactured by Roche.
2. The comparative dissolution testing conducted on the test product, lot# 601-824 (using new raw materials) and on the reference product, lot# 2111 has been found acceptable to the Division of Bioequivalence. There is no change in formulations of two test products produced from two different sources (see table 2, attached). Therefore, the waiver of in vivo bioequivalence study on the test product, lot# 601-824, is granted.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in a medium of 899 ml of water and 1 ml of 0.2 N HCL, at 37°C, using USP XXIII Apparatus II (Paddle) at 50 rpm. The test drug should meet the following specifications:  
Not less than (Q) of the labeled amount of each component of the drug in the dosage form is dissolved in 60 minutes.
4. The firm should be informed of the above comments and recommendations.

Sikta Pradhan, Ph.D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHUANG  
FT INITIALED YCHUAN

Concur:

for Nicholas Fleischer, Ph.D.  
Director, Division of Bioequivalence

cc: ANDA # 74-650AD.N96 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File.

SP/04-08-97/04-16-97/5-5-97/6-5-97/X:\wpfile\Biofinal\74650AD.N96

Table 2

## COMPARISON OF FORMULATIONS

## HI-TECH'S SULFAMETHOXAZOLE AND TRIMETHOPRIM SUSPENSION

(Sulfamethoxazole 200 mg &amp; Trimethoprim 40 mg)

Lots 401-824 and 601-824

and

## ROCHE LABORATORIES' BACTRIM SUSPENSION

	<u>Roche Laboratories Bactrim</u>	<u>Hi-Tech's Sulfamethoxazole &amp; Trimethoprim Oral Suspension Lot 401-824</u>	<u>Hi-Tech's Sulfamethoxazole &amp; Trimethoprim Oral Suspension Lot 601-824</u>
Sulfamethoxazole	200 mg	200 mg	200 mg
Trimethoprim	40 mg	40 mg	40 mg
Also contains:			
	Alcohol 0.3 %	Alcohol 0.26 %	Alcohol 0.26 %
	Methylparaben	Methylparaben	Methylparaben
	Propylparaben	—	—
	Edetate Disodium	—	—
	—	Sodium Benzoate	Sodium Benzoate
	—	Carboxymethyl- cellulose Sodium	Carboxymethyl- cellulose Sodium
	Citric Acid	Citric Acid	Citric Acid
	FD&C Red No. 40	FD&C Red No. 40	FD&C Red No. 40
	FD&C Yellow No. 6	—	—
	—	FD&C Blue No. 1	FD&C Blue No. 1
	Flavors	Grape Flavor	Grape Flavor
	Glycerin	Glycerin	Glycerin
	Microcrystalline Cellulose	Microcrystalline Cellulose	Microcrystalline Cellulose
	Polysorbate 80	Polysorbate 80	Polysorbate 80
	Saccharin Sodium	Saccharin Sodium	Saccharin Sodium
	Sorbitol	Sorbitol	Sorbitol
	Silmethicone	—	—
	Sucrose	—	—
	Purified Water	Purified Water	Purified Water

D.J

FEB 12 1996

**Sulfamethoxazole and  
Trimethoprim Oral Suspension  
200mg/40mg per 5ml  
ANDA #74-650  
Reviewer: Ramona McCarthy  
WP #74650S.395**

**Hi-Tech Pharmacal Co. Inc.  
Amityville, New York  
Submission Dated:  
March 20, 1995  
Amendment: May 10, 1995**

**Review of a Bioequivalence Study and Dissolution Data**

This submission provides for a bioequivalence study on this product as compared with the reference product, Bactrim (trimethoprim and sulfamethoxazole) Suspension. The product contains active ingredients in the same strength and dosage form as the reference listed drug. This formulation differs from the reference product, Bactrim Suspension, in the amount of alcohol, in the preservatives and the flavor.

The composition of the product is as follows:

Each 5ml (teaspoonful) contains:

Sulfamethoxazole, USP	200.0mg
Trimethoprim, USP	40.0mg

Methylparaben, NF

Sodium Benzoate, NF

Microcrystalline Cellulose and

Carboxymethylcellulose Sodium, NF

Glycerin USP

Sodium Saccharin, USP

Sorbitol Solution, USP

Polysorbate 80, NF

Grape Flavor, natural and Artificial

Citric Acid, Anhydrous, USP

FD & C Red No. 40

FD & C Blue No. 1

Alcohol 95%, USP

Equivalent to absolute alcohol

Purified Water, USP

Q.S

The batch size has been stated as being

The objective of the study is to compare the bioavailability of sulfamethoxazole and trimethoprim from the two products tested. The study design is a single dose two-way crossover study employing 20 subjects and a 800mg/160mg in 20ml oral suspension dose.

The study was conducted by the \_\_\_\_\_ as the principal investigator. The study was conducted under the supervision of \_\_\_\_\_ as the principal investigator. The customary informed consent forms were included along with the review by the National Institutional Review Board, which were acceptable.

Clinical dates: Phase 1, 10/20/94-10/22/94; Phase 2, 10/27/94-10/29/94  
Analytical dates: 12/11/94-12/21/94.

The study employed twenty male subjects, 18-60 years of age, not more than  $\pm 15\%$  from ideal weight for his height as defined by Metropolitan Life Insurance Co. The subjects had to be free of any history of asthma, cardiovascular, neurological, hepatic, renal, hematopoietic (particularly megaloblastic anemia) gastrointestinal or on-going infectious disease, alcohol or drug abuse, as evidenced by a medical history and physical examination within 30 days prior to the start of the study. Blood chemistry (alkaline phosphatase, glucose, SGOT, SGPT, LDH, BUN, GGT, creatinine, bilirubin, electrolytes), hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count), and urinalysis values within clinically acceptable limits were performed within 30 days prior to the start of the study. The subjects could have no known allergy to trimethoprim, sulfonamides, or sulfa drugs; no prescription drugs within 14 days, or OTC medications within 7 days of the first drug administration; no alcohol consumption for at least 24 hours prior to drug administration; no caffeine for at least 12 hours prior to dosing. The subjects had to have negative HIV 1, no hepatitis B surface antigen, and urine screen for drugs of abuse within 30 days prior to the start of the study.

The products employed in this study are as follows:

- (1) Test Product - Trimethoprim (40mg/5ml) and Sulfamethoxazole (200mg/5ml)  
Suspension Lot # 401-824  
Manufacturer: Hi-Tech Pharmacal Co.
- (2) Reference Product - Trimethoprim (40mg/5ml) and Sulfamethoxazole (200mg/5ml) (Bactrim) Pediatric Suspension Lot # 2110  
Manufacturer: Roche Laboratories

Potency (Lot # 401-824)

<u>Ingredient</u>	<u>Limits</u>	<u>Results</u>	<u>Mean</u>
Sulfamethoxazole		102.7% 101.3% 102.3%	102.25%
Trimethoprim		103.2% 102.4% 100.3%	101.9%

The subjects were dosed as follows:

The subjects fasted for no fewer than 10 hours prior to drug administration and until 5 hours postdose. 800mg sulfamethoxazole and 160mg trimethoprim (20ml of suspension) was administered at 0 hour with 240ml of water. 15ml venous blood was taken in Vacutainers with no anticoagulant at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours (15 samples). An additional 15ml sample was taken at zero hour of phase 1. The serum was separated, transferred to labeled tubes, and promptly frozen at - 20°C for analysis.



reassayed.

#### Pharmacokinetic and Statistical Analysis

The statistical analysis was performed at \_\_\_\_\_ using SAS version 6.08 and PROC GLM for the ANOVA. All parameters were analyzed by ANOVA and the F - test to determine statistically significant ( $\alpha=0.05$ ) differences between the drug formulations.

Twenty subjects enrolled in the study and completed the clinical portion of the study. All of their serum samples were assayed. Twenty sets of data were used in the analyses for sulfamethoxazole and trimethoprim.

The serum levels of sulfamethoxazole and trimethoprim were measured for 36 hours after drug administration. They were used to calculate the area under the concentration-time curve (AUC) by linear interpolation between consecutive drug levels. AUC 0-T was calculated from zero to the last non-zero concentration C(T). AUC 0-Infinity was calculated by extrapolation of AUC 0-T by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last five concentrations versus time. Half-life ( $HL=\ln 2/KE$ ), C<sub>Max</sub>, T<sub>MAX</sub> and C<sub>MAX</sub>/AUC 0-INF were also reported.

All parameters, including the logarithmic transformations of AUC, C<sub>MAX</sub>, and C<sub>MAX</sub>/AUC 0-INF were analyzed by ANOVA using Type III sum of squares to determine statistically significant differences ( $\alpha=0.05$ ). The least squares means are computed using the general linear model with effects for sequence, subject nested within sequence, phase and drug.

The power of the study to detect a 20% difference in parameters as statistically significant ( $\alpha=0.05$ ) was calculated using the sample estimates and significance level of the central Student's t-distribution.

The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA. The detailed analyses and tabulations are presented in Statistical Appendix I.

## Results

### Sulfamethoxazole

The concentration of sulfamethoxazole at each time point is summarized in Table A. There were significant ( $\alpha=0.05$ ) differences in mean concentrations between the formulations at 0.5, 1, 1.5, 2 and 4 hours after dosing. The time courses of sulfamethoxazole concentration after the two products are plotted and shown in Figure 1 (attached).

The arithmetic mean  $\pm$  standard deviation for each parameter is tabulated in Table 1 (attached) and the results of the analysis of variance are presented in Table 2 (attached). There were statistically significant differences between the formulations for AUC O-T, LNAUC O-T, AUC O-INF, LNAUC O-INF, C<sub>MAX</sub>, LNC<sub>MAX</sub>, and KE. Based on the least squares means of the logarithmically transformed parameters, the AUC O-T and AUC O-INF for the test product were 7% and 6% lower than the respective estimates for the reference product. The C<sub>MAX</sub> for the test product was 7% lower than that for the reference product and occurred at the same time. Based on the logarithmic transformation, the 90% confidence intervals about the ratios of test/reference means for AUC O-T, AUC O-INF and C<sub>MAX</sub> were within the 0.8-1.25 limit when the Hi-Tech suspension was compared to the Roche suspension (AUC O-T [0.91; 0.96], AUC O-INF [0.92; 0.96], and C<sub>MAX</sub> [0.90; 0.97]).

### Trimethoprim

The concentration of trimethoprim at each time point after each product is summarized in Table B. There were significant ( $\alpha=0.05$ ) differences in mean concentrations between the formulations at 0.5 and 10 hours after dosing. The time courses of trimethoprim concentration after the two products are plotted (Figure 2 attached). The arithmetic mean  $\pm$  standard deviation for each parameter is tabulated in Table 3 and the results of the analysis of variance are presented in Table 4 (both are attached). There were statistically significant differences between the formulations for C<sub>MAX</sub>, LN C<sub>MAX</sub>, KE, C<sub>MAX</sub>/AUC O-INF, and LN C<sub>MAX</sub>/AUC O-INF.

A significant sequence effect ( $\alpha=0.10$ ) was observed for the trimethoprim AUC O-T, LN AUC O-T, AUC O-INF and LNAUC O-INF. The guidance "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" states that a statistically significant sequence effect may be acceptable provided (1) it is a single dose study; (2) it includes only healthy, normal subjects; (3) the drug is not an endogenous entity; and (4) a more than adequate wash-out period has been allowed between the phases of the study, and in the second phase, the pre-dose biological matrix samples do not exhibit any detectable drug level in all subjects. This study meets all these requirements.

Based on the least squares means of the logarithmically transformed parameters, the AUC o-t and AUC O-INF for the test product were 2% and 3% higher than the respective estimates for the reference product. The CMAX for the test product was 5% lower than that for the reference product and occurred 29% later (2.1 hr versus 1.6 hr). Based on the logarithmic transformation, the 90% confidence intervals about the ratios of test/reference means for AUC O-T, AUC O-INF and CMAX were within the 0.80 - 1.25 limit when the Hi-Tech suspension was compared to the Roche suspension, (AUC O-T [0.99; 1.06], AUC O-INF [1.00; 1.07], and CMAX [0.92; 0.99]).

#### Comments

1. The results indicate that the 90% confidence intervals for AUC O-T, AUC O-INF and CMAX for both the sulfamethoxazole and trimethoprim are all within the acceptable range, based on the logarithmic transformation.
2. Accordingly, the study has been found acceptable. However, the application is incomplete from a bioequivalence point of view, in that there was an omission of comparative dissolution data.

#### Recommendation

The firm should be advised as follows:

1. The bioequivalence study conducted by Hi-Tech Pharmacal Co, Inc. on its Sulfamethoxazole and Trimethoprim Oral Suspension, 200mg/400mg per 5ml, Lot #401-824, comparing it to Bactrim (Sulfamethoxazole and Trimethoprim) Oral Suspension, 200mg/400mg/5ml manufactured by Roche Laboratories, has been found incomplete by the Division of Bioequivalence. The application is incomplete from the bioequivalence point of view, in that there was an omission of comparative dissolution data.
2. Comparative dissolution testing must be performed on 12 individual dosage units of both the reference product and test product, employing the same lots

used in the bioequivalence study. The testing should be conducted in a medium of 899 ml of water and 1 ml of 0.2 N HCL, at 37°C, using USP XXIII Apparatus II (Paddle) at 50 rpm, at 15,30,45 and 60 minutes. All raw data should be submitted along with the means, range and % RSD at each sampling interval.

✓  
for  
Ramona M. Hawkins  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHUANG  
FT INITIALED YCHUANG

Date

2/8/96

Concur:

Date

2/12/96

Keith K. Chan, Ph.D  
Director  
Division of Bioequivalence

cc: ANDA # 74-650 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Hawkins), Drug File, Division File

RMH/dmb/120895/WP # 74650S.395

**Table A-Mean Sulfamethoxazole Serum Levels (mcg/ml)**

**(after 800mg/20ml Oral Suspension Dose)**

Time (hrs)	Test (*)	S.D	Reference (**)	S.D.
0	0.00	0.00	0.00	0.00
0.5	28.95	13.65	38.80	17.20
1.0	38.53	13.06	44.43	13.80
1.5	41.12	13.39	48.54	12.46
2.0	44.11	13.45	48.81	10.42
2.5	45.42	8.18	49.83	12.10
3.0	45.37	8.04	47.05	9.30
4.0	41.29	5.05	43.57	6.31
6.0	35.06	5.53	36.75	6.11
8.0	30.66	5.55	32.24	6.57
10.0	26.71	4.57	26.60	5.22
12.0	21.47	3.87	21.88	4.72
16.0	16.39	3.48	17.60	4.96
24.0	10.48	2.98	10.86	3.25
36.0	4.62	2.08	4.82	2.05

\*Hi-Tech Product

\*\*Roche Product (Bactrim)

**Mean Pharmacokinetic Parameters**

Parameter	Test	CV (%)	Reference	CV (%)	Test/ Reference
AUC (mcg ml <sup>1</sup> hr)	667.0	19.0	715.7	19.9	0.93
AUC O-INF mcg ml <sup>1</sup> hr	745.7	22.3	793.6	23.1	0.94
C <sub>MAX</sub> mcg/ml	51.22	17.7	55.10	21.4	0.93
T <sub>MAX</sub> (hr)	1.875	39.5	1.875	47.3	1.00
HALF Life (hr)	10.34	18.3	10.66	14.1	0.97
Rate Constant (hr <sup>-1</sup> )	0.0690	16.7	0.0661	13.0	1.04

**Table B.-Mean Trimethoprim Serum Levels \*(mcg/ml)**

Time (hrs)	Test +	S.D.	Reference ++	S.D.
0				
0.5	0.870	0.353	1.171	0.473
1.0	1.397	0.274	1.519	0.423
1.5	1.469	0.307	1.555	0.301
2.0	1.460	0.271	1.511	0.272
2.5	1.430	0.226	1.547	0.371
3.0	1.424	0.217	1.459	0.271
4.0	1.296	0.171	1.309	0.184
6.0	1.095	0.155	1.086	0.173
8.0	0.971	0.168	0.953	0.159
10.0	0.861	0.136	0.816	0.130
12.0	0.686	0.123	0.665	0.150
16.0	0.531	0.127	0.501	0.125
24.0	0.309	0.100	0.284	0.103
36.0	0.113	0.105	0.081	0.103

\*After 160 mg/20ml Oral Suspension

+Hi-Tech Product

++Roche Product (Bactrim)

**Mean Pharmacokinetic Parameters**

Parameter	Test	CV (%)	Reference	CV (%)	Test/ Reference
AUC (mcg ml <sup>-1</sup> hr)	20.49	20.2	20.06	20.6	1.02
AUC O-INF mcg ml <sup>-1</sup> hr	23.53	21.4	22.84	22.0	1.03
C <sub>MAX</sub> mcg/ml	1.62	19.3	1.71	21.0	0.95
T <sub>MAX</sub> (hr)	2.10	33.3	1.63	44.5	1.29
HALF Life (hr)	10.01	27.1	9.51	30.4	1.05
Rate Constant (hr <sup>-1</sup> )	0.0734	23.3	0.0787	27.2	0.93

Figure 1: Mean Sulfamethoxazole Serum Levels

n = 20

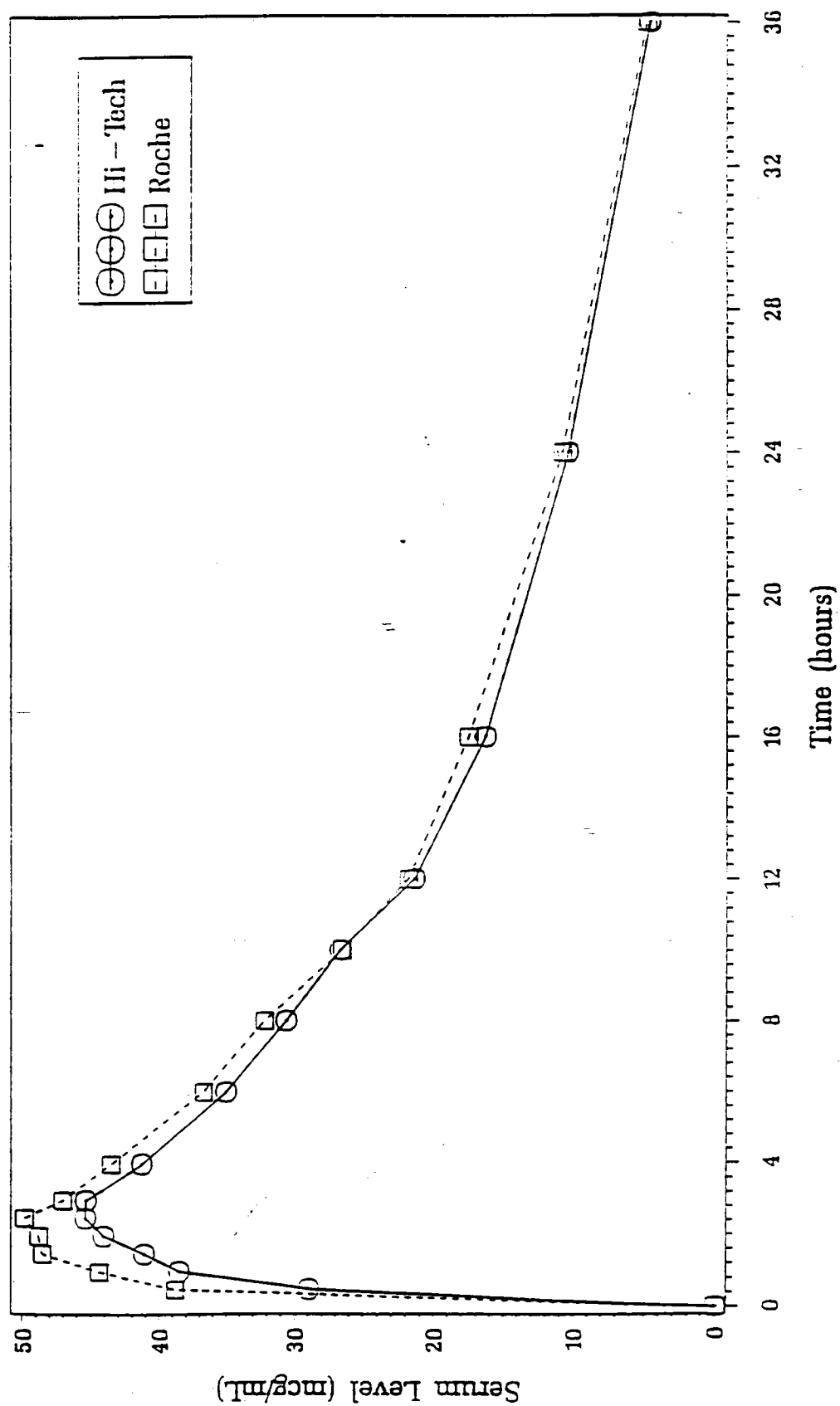


TABLE 1: SULFAMETHOXAZOLE SERUM CONCENTRATIONS  
ARITHMETIC MEANS  $\pm$  STANDARD DEVIATION  
(mcg/mL)

Time (Hours)	Hi-Tech		Roche		Ratio Test/Reference	Significance
	Test Product	Reference Product	Test/Reference	Significance		
0	0.0000	0.0000	--	--		
0.5	28.95 ± 13.65	38.80 ± 17.20	0.75	p<0.05		
1	38.53 ± 13.06	44.43 ± 13.80	0.87	p<0.05		
1.5	41.12 ± 13.39	48.54 ± 12.46	0.85	p<0.05		
2	44.11 ± 13.45	48.81 ± 10.42	0.90	p<0.05		
2.5	45.42 ± 8.178	49.83 ± 12.10	0.91	N.S.		
3	45.37 ± 8.039	47.05 ± 9.302	0.96	N.S.		
4	41.29 ± 5.051	43.57 ± 6.312	0.95	p<0.05		
6	35.06 ± 5.531	36.75 ± 6.114	0.95	N.S.		
8	30.66 ± 5.552	32.24 ± 6.573	0.95	N.S.		
10	26.71 ± 4.574	26.60 ± 5.217	1.00	N.S.		
12	21.47 ± 3.867	21.88 ± 4.725	0.98	N.S.		
16	16.39 ± 3.481	17.60 ± 4.957	0.93	N.S.		
24	10.48 ± 2.985	10.86 ± 3.249	0.97	N.S.		
36	4.617 ± 2.078	4.816 ± 2.047	0.96	N.S.		

TABLE 2: PHARMACOKINETIC PARAMETERS  
LEAST SQUARES MEANS  $\pm$  STANDARD ERROR  
SERUM SULFAMETHOXAZOLE

Parameter	Test Hi-Tech	Reference Roche	Test/ Reference	Significance	Study Power	Intrasubject C.V. (%)	90% Confidence Interval
AUC 0-T (mcg mL <sup>-1</sup> hr)	667.0 $\pm$ 7.830	715.7 $\pm$ 7.830	0.93	p=0.0003	>0.99	4.9	0.91, 0.96
Ln AUC 0-T (Antiln)	6.4870 $\pm$ 0.0109 (656.6)	6.5564 $\pm$ 0.0109 (703.7)	0.93	p=0.0003	>0.99	4.9	0.91, 0.96
AUC 0-Inf (mcg mL <sup>-1</sup> hr)	745.7 $\pm$ 8.537	793.6 $\pm$ 8.537	0.94	p=0.0009	>0.99	4.8	0.91, 0.97
Ln AUC 0-Inf (Antiln)	6.5938 $\pm$ 0.0102 (730.5)	6.6547 $\pm$ 0.0102 (776.5)	0.94	p=0.0005	>0.99	4.6	0.92, 0.96
Cmax (mcg/mL)	51.22 $\pm$ 1.014	55.10 $\pm$ 1.014	0.93	p=0.0144	>0.99	8.2	0.88, 0.97
Ln Cmax (Antiln)	3.9217 $\pm$ 0.0161 (50.49)	3.9895 $\pm$ 0.0161 (54.03)	0.93	p=0.0079	>0.99	7.2	0.90, 0.97
Tmax (hr)	1.875 $\pm$ 0.1525	1.875 $\pm$ 0.1525	1.00	N.S.	<0.50	36.4	0.80, 1.20
Rate Constant (hr <sup>-1</sup> )	0.06901 $\pm$ 0.00091	0.06612 $\pm$ 0.00091	1.04	p=0.0373	>0.99	6.1	1.01, 1.08
Half-Life (hr)	10.34 $\pm$ 0.1534	10.66 $\pm$ 0.1534	0.97	N.S.	>0.99	6.4	0.93, 1.00
Cmax/ AUCI	0.07003 $\pm$ 0.00119	0.07038 $\pm$ 0.00119	0.99	N.S.	>0.99	7.5	0.95, 1.04
Ln (Cmax/AUCI) (Antiln)	-2.6721 $\pm$ 0.0157 (0.06911)	-2.6653 $\pm$ 0.0157 (0.06958)	0.99	N.S.	>0.99	7.0	0.96, 1.03

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant ( $\alpha=0.05$ ), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

Figure 2: Mean Trimethoprim Serum Levels

$n = 20$

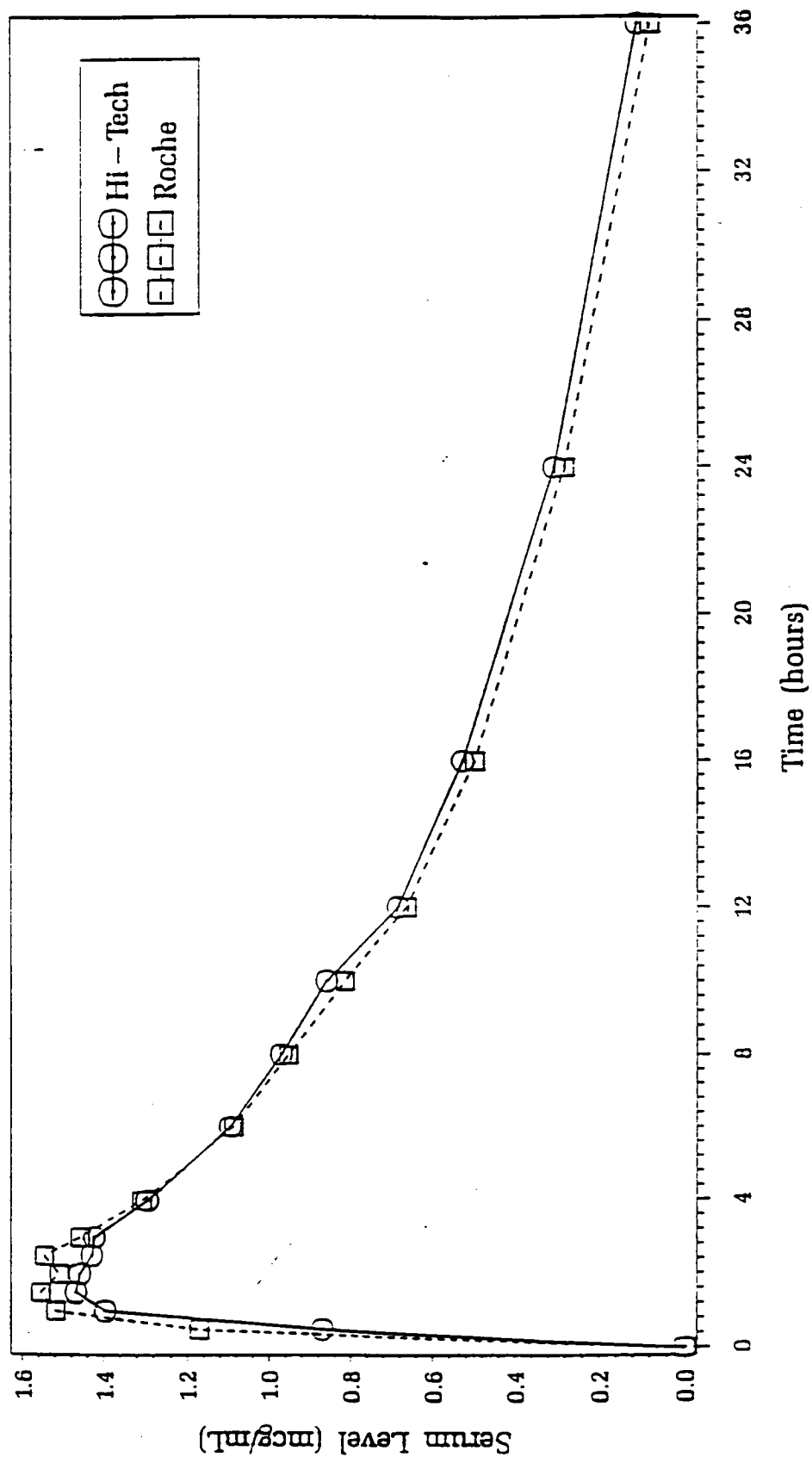


TABLE 3. TRIMETHOPRIM SERUM CONCENTRATIONS  
ARITHMETIC MEANS  $\pm$  STANDARD DEVIATION  
(mcg/mL)

Time (Hours)	Hl-Tech		Roche		Ratio	
	Test Product	Reference Product	Test/Reference	Significance		
0	0.0000	0.0000				
0.5	0.8700 $\pm$ 0.3528	1.171 $\pm$ 0.4735	0.74		p<0.05	
1	1.397 $\pm$ 0.2740	1.519 $\pm$ 0.4233	0.92		N.S.	
1.5	1.469 $\pm$ 0.3069	1.555 $\pm$ 0.3013	0.94		N.S.	
2	1.460 $\pm$ 0.2709	1.511 $\pm$ 0.2718	0.97		N.S.	
2.5	1.430 $\pm$ 0.2256	1.547 $\pm$ 0.3709	0.92		N.S.	
3	1.424 $\pm$ 0.2168	1.459 $\pm$ 0.2711	0.98		N.S.	
4	1.296 $\pm$ 0.1714	1.309 $\pm$ 0.1842	0.99		N.S.	
6	1.095 $\pm$ 0.1550	1.086 $\pm$ 0.1731	1.01		N.S.	
8	0.9715 $\pm$ 0.1687	0.9534 $\pm$ 0.1591	1.02		N.S.	
10	0.8612 $\pm$ 0.1365	0.8156 $\pm$ 0.1297	1.06		p<0.05	
12	0.6861 $\pm$ 0.1233	0.6650 $\pm$ 0.1499	1.03		N.S.	
16	0.5309 $\pm$ 0.1265	0.5010 $\pm$ 0.1250	1.06		N.S.	
24	0.3087 $\pm$ 0.1003	0.2843 $\pm$ 0.1039	1.09		N.S.	
36	0.1128 $\pm$ 0.1053	0.0812 $\pm$ 0.1026	1.39		N.S.	

TABLE 4: PHARMACOKINETIC PARAMETERS  
LEAST SQUARES MEANS ± STANDARD ERROR  
SERUM TRIMETHOPRIM

Parameter	Test Hl-Tech	Reference Roche	Test/ Reference	Significance	Study Power	Intrasubject C.V. (%)	90% Confidence Interval
AUC 0-T (mcg mL <sup>-1</sup> hr)	20.49 ± 0.3123 (20.12)	20.06 ± 0.3123 (19.65)	1.02	N.S.	>0.99	7.0	0.98, 1.06
Ln AUC 0-T (Antlin)	3.0016 ± 0.0154 (20.12)	2.9783 ± 0.0154 (19.65)	1.02	N.S.	>0.99	6.9	0.99, 1.06
AUC 0-Inf (mcg mL <sup>-1</sup> hr)	23.53 ± 0.3406	22.84 ± 0.3406	1.03	N.S.	>0.99	6.7	0.99, 1.07
Ln AUC 0-Inf (Antlin)	3.1380 ± 0.0148 (23.06)	3.1069 ± 0.0148 (22.35)	1.03	N.S.	>0.99	6.6	1.00, 1.07
Cmax (mcg/mL)	1.623 ± 0.02686	1.709 ± 0.02686	0.95	p=0.0362	>0.99	7.0	0.91, 0.99
Ln Cmax (Antlin)	0.4672 ± 0.0142 (1.596)	0.5166 ± 0.0142 (1.676)	0.95	p=0.0244	>0.99	6.4	0.92, 0.99
Tmax (hr)	2.100 ± 0.1713	1.625 ± 0.1713	1.29	N.S.	<0.50	47.1	1.03, 1.55
Rate Constant (hr <sup>-1</sup> )	0.07340 ± 0.00174	0.07865 ± 0.00174	0.93	p=0.0470	>0.99	9.9	0.88, 0.99
Half-life (hr)	10.01 ± 0.2204	9.506 ± 0.2204	1.05	N.S.	>0.99	10.4	1.00, 1.11
Cmax/ AUCI	0.07067 ± 0.00143	0.07672 ± 0.00143	0.92	p=0.0079	>0.99	8.4	0.88, 0.97
Ln (Cmax/AUCI) (Antlin)	-2.6708 ± 0.0196 (0.06919)	-2.5903 ± 0.0196 (0.07500)	0.92	p=0.0095	>0.99	8.8	0.88, 0.97

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant ( $\alpha=0.05$ ), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

October 4, 1996

AMENDMENT  
NAC

Rashmikanth M, Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food & Drug Administration  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

Re: Major Amendment to Pending ANDA  
Product: Sulfamethoxazole and Trimethoprim Oral Suspension USP  
200 mg/40 mg per 5 mL  
ANDA 74-650

Dear Dr. Patel:

Reference is made to our abbreviated new drug application dated March 20, 1995, our amendment dated May 8, 1995 and your letter dated March 4, 1996.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora

Elan Bar-Giora  
Executive Vice President

EB:jc  
Enc.



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

September 3, 1997

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food & Drug Administration  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

**WIA ORIG AMENDMENT**

*WAC*

Re: **Telephone Amendment**  
Sulfamethoxazole & Trimethoprim Oral Suspension USP  
ANDA 74-650

Dear Sir:

Reference is made to the above cited abbreviated new drug application and our telephone conversation of September 3, 1997 with Mr. Jim Wilson, Project Manager.

As per Mr. Wilson's request, submitted herewith are Method-149-2 (Specifications for In-Process, Finished Product Release and Stability Testing of Sulfamethoxazole and Trimethoprim Oral Suspension, USP) revised to include the following dissolution specifications:

Not less than (Q) of the labeled amount of each component of the drug in the dosage form is dissolved in 60 minutes.

Additionally, we are enclosing a stability protocol and finished product specifications revised to include dissolution testing.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228, extension 108.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora  
Executive Vice President

EB:jc  
Enc.

**RECEIVED**

SEP 4 - 1997

**GENERIC DRUGS**



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

September 4, 1997

NDA CRIL AMENDMENT

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food & Drug Administration  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

N/AC

Re: **Telephone Amendment**  
Sulfamethoxazole & Trimethoprim Oral Suspension USP  
ANDA 74-650

Dear Sir:

Reference is made to the above cited abbreviated new drug application and our telephone conversation of September 4, 1997 with Mr. Jim Wilson, Project Manager and Dr. V. Sayeed.

As per Dr. Sayeed's request, submitted herewith are stability specifications for Sulfamethoxazole and Trimethoprim Oral Suspension, USP.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228, extension 108.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora  
Executive Vice President

EB:jc  
Enc.

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SEP 5 - 1997  
GENERIC DRUGS



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

NOTED  
5/13/97  
*[Signature]*

May 1, 1997

NEW CORRESP  
*NC*

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food & Drug Administration  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

Re: General Correspondence to Pending ANDA  
Product: Sulfamethoxazole/Trimethoprim Oral  
Suspension USP 200 mg/40 mg per 5 mL  
ANDA 74-650

Dear Sir:

Reference is made to the above abbreviated new drug application dated March 20, 1995 and our major amendment dated April 30, 1997.

Hi-Tech used Sulfamethoxazole and Trimethoprim manufactured by \_\_\_\_\_ to produce the exhibit batch submitted in this abbreviated new drug application. \_\_\_\_\_ had an explosion in their facility during April, 1995.

In a major amendment dated March 4, 1996 (almost one year after submission) the agency recommended that Hi-Tech amend the application to provide for new sources of the two active drug substances. Hi-Tech addressed all of the agency's concerns in the major amendment on October 4, 1996 (except for the new exhibit batch) and submitted all of the information relative to the new batch in a major amendment dated November 27, 1996.

In response to our major amendments of October 4 and November 27, Hi-Tech received another major amendment dated April 18, 1997 with revisions to the package insert and only eight minor chemistry comments - and most of the comments are asking for clarification of manufacturing instructions which Hi-Tech feels could have been answered in a telephone call or at most, a minor amendment.

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MAY 05 1997

GENERIC DRUGS

*7/1/97*  
*5/13/97*

Page Two  
Director, Office of Generic Drugs  
May 1, 1997

In view of the above, Hi-Tech respectfully requests the agency to reconsider and change this major amendment to a minor amendment. This product is very important to Hi-Tech. Thank you for your cooperation.

Sincerely,

HI-TECH PHARMACAL CO., INC.

A handwritten signature in dark ink, appearing to read "Elan Bar-Giora". The signature is fluid and cursive, with the first name "Elan" being more prominent.

Elan Bar-Giora  
Executive Vice President

EB:jc



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

April 30, 1997

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food & Drug Administration  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

*Label*  
NDA ORAL AMENDMENT  
*HC*

Re: Major Amendment to Pending ANDA  
Product: Sulfamethoxazole/Trimethoprim Oral  
Suspension USP 200 mg/40 mg per 5 mL  
ANDA 74-650

Dear Sir:

Reference is made to the above abbreviated new drug application, our amendment dated November 27, 1996 and the agency's major amendment dated April 18, 1997.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

*Elan Bar-Giora*

Elan Bar-Giora  
Executive Vice President

EB:jc  
Enc.

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MAY 11 1997

GENERIC DRUGS

*Nadine*  
*5-4-97*



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

November 27, 1996

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855

**MAJOR AMENDMENT**

Re: Major Amendment to Pending ANDA  
Product: Sulfamethoxazole and Trimethoprim Oral Suspension  
200 mg/40 mg per 5 mL  
ANDA 74-650

Dear Sir:

Reference is made to the above mentioned abbreviated new drug application dated March 20, 1995 for Sulfamethoxazole and Trimethoprim Oral Suspension, the agency's major amendment dated March 4, 1996 and Hi-Tech's response to that amendment dated October 4, 1996.


As recommended in comment A4 of the March 4, 1996 FDA letter, Hi-Tech is amending our application to provide for new sources of the two active drug substances. Submitted in this amendment is all of the information relative to the new exhibit batch manufactured using the new source drug substances. This new exhibit batch meets the requirements of the original batch. Draft labeling revised in accordance with the agency's recommendations of March 4, 1996 was submitted in our major amendment dated October 4, 1996. The packaging components are exactly the same those as previously submitted.

Following this cover letter, please find all of the information relative to the new exhibit batch. This submission contains an archival copy (two volumes) and a review copy (two volumes).

If you have any questions concerning this amendment, please contact Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

  
Elan Bar-Giora  
Executive Vice President

EB:jc

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DEC 03 1996



PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701

(516) 789-8228

May 8, 1995

AMENDMENT

N/A

Ms. Yana Ruth Mille  
Acting Director  
Division of Labeling & Program Support  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
FOOD & DRUG ADMINISTRATION  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20855-2773

RE: ANDA 74-650  
SULFAMETHOXAZOLE & TRIMETHOPRIM ORAL SUSPENSION USP  
200 mg/40 mg per 5 mL

Dear Madam:

Reference is made to the agency's communication dated April 24, 1995 in which you refuse to file this ANDA under 21 CFR 314.101 (d)(3) because we have failed to address the marketing exclusivity granted to the listed drug.

Enclosed please find a revised exclusivity statement and four copies of draft insert labeling revised to eliminate this indication.

Additionally, we are enclosing a side-by-side comparison of our proposed labeling with differences annotated and explained.

If you have any questions concerning the submitted information, please contact Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

*Elan Bar-Giora*

Elan Bar-Giora  
Executive Vice President

EB:jc  
Enc.

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MAY 10 1995

GENERIC DRUGS



PHARMACAL CO., INC.

*Refer to file 4/3/95*  
369 BAYVIEW AVENUE, AMITYVILLE, N.Y. 11701  
(516) 789-8228

March 20, 1995

Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
FOOD & DRUG ADMINISTRATION  
Metro Park North II  
HFD-600, Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

**RE: SULFAMETHOXAZOLE & TRIMETHOPRIM ORAL SUSPENSION**

Dear Sir:

Pursuant to 21 CFR part 314.92, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting an Abbreviated New Drug Application for Sulfamethoxazole and Trimethoprim Oral Suspension. This submission contains an archival copy (six volumes) and a review copy (six volumes) in addition to a method validation package.

The product is an oral suspension which contains active ingredients in the same strength and dosage form as the reference listed drug, Bactrim Suspension (Roche's NDA 17-560). The formulation of Hi-Tech's product differs from Bactrim in the amount of alcohol, in the preservatives and the flavor. This product was formulated to closely resemble Septra Grape Suspension manufactured by Burroughs Wellcome, also listed in the Approved Drug Products with Therapeutic Equivalence Evaluations, 14th Edition with an AB rating. The reference listed drug, Bactrim, identified in the Approved Drug Products with Therapeutic Equivalence Evaluations, 14th Edition is listed with a bioequivalence rating of AB.

The labeling of the new drug is the same as that of Bactrim for changes that are necessary due to a change in the manufacturer and the above listed ingredient differences.

Following this cover letter, please find the Certification required by the Generic Drug Enforcement Act of 1992, and the Office of Generic Drugs letter dated January 15, 1993 and our certification that a true copy of this application has been submitted to the New York District Office. The required patent certification information to show that the drug product provided in this application is the same as the listed drug and a completed Form FDA 356h are also included.

If you have any questions concerning this ANDA, please contact Elan Bar-Giora at 516-789-8228. We look forward to your prompt review of the submitted information.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora  
Executive Vice President

Enc.

RECEIVED

MAR 24 1995

GENERIC DRUGS